REMARKS

Applicants respectfully request reconsideration of the Office Action mailed on November 12, 2003 and allowance of the claims.

Claims, 1, 4, 5, and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deninno, et al. (WO 00/17164) in view of Roth (U.S. Patent No. 4,681,893) for the reasons of record in the previous Office Action dated September 6, 2002 at pages 2-3.

The rejection states that the difference between the references and applicant's claimed subject matter lies in that Deninno, et al. teach only the compound atorvastatin and not the presently claimed salts and/or hydroxy acid forms thereof.

The rejection also states that to the skilled artisan, applicant's claimed subject matter would have been obvious because Roth teaches the presently claimed salt forms and hydroxy acid forms of atorvastatin (see the abstract, column 2, line 3-43 and column 7, line 1-17) as being effective HMG-CoA reductase inhibitors and the skilled artisan would have been motivated to alternatively use the compounds of Roth for the same purpose as the atorvastatin of Dennino et al. because Dennino et al teaches atorvastatin for its HMG-CoA reductase inhibitory activity and Roth identified his compounds as being HMG-CoA reductase inhibitors. The rejection also states that Applicants' allegation of "benefits" amounts to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. The rejection also states that it has not been established on the record, by means of comparative experimental data, that Applicants' combination produces any results that would not have been obvious from the prior art teachings.

Applicant traverses the 35 U.S.C. §103 rejection of the claims and respectfully request that the Examiner withdraw the rejection and allow the claims.

Applicant's claims are directed to a pharmaceutical composition comprising specific drugs, hydroxy-substituted atorvastatin and [2R, 4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (hereinafter "the compound"), in the form of a single composition. Applicant discovered that of all the many broad classes of drug substances, and the far greater number of individual drugs within those classes,

that have been suggested for use in the field of cardiovascular care, these active chemicals, when used together in combination with a pharmaceutically acceptable carrier, vehicle or diluent, provide benefits in the treatment of certain medical conditions.

While each of these individual drugs was known *per se* and was used alone for certain medicinal purposes, such as reflected in the cited references, their specific use together in a fixed composition has not been described in the prior art cited by the Examiner for any reason whatsoever. Applicant's claims have been rejected only as obvious (35 USC §103), and the Examiner has effectively conceded the novelty of the claimed composition.

Thus, we start the patentability analysis with the fact that no one ever before combined these active ingredients into a single pharmaceutical composition. The Examiner contends, however, that the combination of the hydroxy-substituted atorvastatin and "the compound" in a single pharmaceutical composition is *prima facie* obvious.

While Applicant appreciates the explanations provided by the Examiner, Applicant respectfully traverses this obviousness conclusion and urges reconsideration and withdrawal. There is no teaching or suggestion in the art that these particular drugs should be selected from the vast array of available compounds and combined in a single pharmaceutical composition, and there is no reasonable expectation of success (i.e., any benefit) taught by the art were that to be done. At best, the art supports only an "obvious to try" situation (which Applicant does not concede).

In presenting this argument regarding "obvious to try," Applicant submits that for *prima facie* obviousness to exist (see MPEP §2142) for the combination of hydroxy-substituted atorvastatin and "the compound" in a single pharmaceutical composition, there must be a motivation for making such a composition. Some reason must exist from the teachings of the references (and not via hindsight) to select these specified ingredients and put them together in a single pharmaceutical composition. It is not enough simply to say that there is a general teaching or desire to combine materials -- instead, one skilled in the art must be motivated by some teaching in the art to make the specific combination claimed. And, assuming such motivation (which Applicant submits does not exist here), additionally and separately, the art must teach a reasonable expectation of a successful result. The Examiner

has the initial burden to establish both motivation and reasonable expectation. Restated, the law is clear that the Examiner must first establish, from the art, the motivation to select the ingredients and establish a reasonable expectation of success. If the rejection does not provide both, Applicant is under no obligation to rebut any presumption, e.g., by providing evidence of an unexpected result. MPEP §2142.

In short, the cited references simply do not establish *prima facie* obviousness under the legal requirements of 35 U.S.C. §103 as established by MPEP, the applicable statute and the decided case law. Consequently, Applicant respectfully requests that the obviousness rejections will be withdrawn, and this application be passed to issue.

The Federal Circuit's admonition that combinations of old elements (*i.e.*, elements *per se* taught in the art even for the same purpose as claimed) can still be patentable was restated in *The Gillette Company v. S.C. Johnson & Son, Inc.*, 15 U.S.P.Q.2d 1923 (Fed. Cir. 1990):

> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. *What must be found obvious to defeat the patent is the claimed combination.*

And the Court carefully distinguished the legal standard of obviousness from "obvious to try":

> [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *** However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103.

See also In re Fine, 5 U.S.P.Q.2d 1596, 1598-9 (Fed. Cir. 1988) (no *prima facie* obviousness; "obvious to try" is "not a legitimate test of patentability"); *In re Jones*, 21 U.S.P.Q. 1941 (Fed. Cir. 1992) (no *prima facie* obviousness even though the prior art generically taught Applicants' claimed substituted amine salt of dicamba and the

specific salt moiety was known for other acids); *Ecolochem, Inc. v. Southern California Edison Co.*, 56 U.S.P.Q.2d 1065, 1072-3 (Fed. Cir. 2000); *In re Antonie,* 195 U.S.P.Q. 6, 8 (CCPA 1977) and *In re Tomlison*, 150 U.S.P.Q. 623, 626 (CCPA 1966).

Applicant also respectfully refers the Examiner to the MPEP, Section 2142, where the legal concept of *prima facie* obviousness is explained in detail with applicable illustrations and cited authority. As stated there:

1. The concept of *prima facie* obviousness is a "procedural tool of examination" which "allocates who has the burden of going forward with production of evidence in each step of the examination process";

2. The Examiner "bears the initial burden of factually supporting any *prima facie* conclusion of obviousness";

3. If the Examiner "does not produce a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness"; and

4. In determining whether a *prima facie* case of obviousness exists, the Examiner is cautioned "that impermissible hindsight must be avoided and the legal conclusion [of *prima facie* obviousness] must be reached on the basis of the facts gleaned from the prior art".

MPEP §2142 further advises as follows regarding what is required before the Examiner can establish *prima facie* obviousness:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure."

See also MPEP §§2143 et seq and the legal authorities and factual examples there set forth.

With these admonitions from the Federal Circuit, the MPEP and its cited supporting case law in mind, Applicant submits that the threshold issue becomes whether the Examiner has carried the burden to establish *prima facie* obviousness

from the cited references -- is there something in the art that motivates a skilled worker to combine the claimed specific materials into a single pharmaceutical composition coupled with a reasonable expectation that if this were done, a beneficial result would be obtained?

Applicant respectfully admits that the answer is "no" as to both issues, and therefore no case of *prima facie* obviousness has been established. Thus, this application should be passed promptly to issue.

Further, the motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

Again, the rejection does not detail reasoning that provides the motivation to modify the prior art and thus the rejection does not present a *prima facie* case of obviousness.

Thus, there is no motivation that the combination of the hydroxy-substituted atorvastatin and "the compound" would be useful for the treatment of atherosclerosis, and there is no reasonable expectation of success taught by the art were such agents to be tried for the treatment of atherosclerosis. At best, the art supports only an "obvious to try" situation.

Applicants submit their invention is not "obvious to try", but even assuming arguendo, that the claims are "obvious to try" that is not the standard for patentablity.

It is Applicants' position that "obvious to try" is not the standard for patentability, and that the Examiner did not make out a *prima facie* case because, *inter alia* (1) the references provide no effective motivation or suggestion that the administration of the specific combination could or would be useful for the treatment of atherosclerosis and (2) even allowing, *arguendo*, that any such suggestion or motivation is provided, the references provide absolutely no expectation of success. The law is emphatic that "obvious to try" is not the standard for patentability.

"Obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

The art cited by the Examiner, at most, makes it no more than perhaps obvious to explore the area of combinations generally, and this is one of the classic hallmarks of an "obvious to try" rejection:

> "The admonition that 'obvious to try' is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**"

In re O'Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

It is further noted that "[t]he issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. It is only that hypothetical person who is presumed to be aware of all the prior art. The actual inventor's skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will -- which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under section 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of

references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which." Standard Oil Co. V. American Cyanamid Co., 774 F.2d 448, 454 (Fed. cir. 1985).

Further, even if the art is, *arguendo*, viewed as providing a suggestion, it provides no reasonable expectation or likelihood of success. Thus, even if an argument could be made that the art provides a suggestion to explore the use of such combinations generally to treat atherosclerosis, this amounts, perhaps, to inviting experimentation, i.e., to perhaps making testing such compounds obvious to try, which again is manifestly not the standard for patentability. O'Farrell, supra.

The points and concerns raised by the Examiner having been fully addressed. Applicants urge that this application is in condition for allowance, which action is respectfully requested.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

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